

B7
46. The compound of claim 45 wherein B is guanine, adenine, cytosine, uracil, 5-fluorouracil, 5-iodouracil, thymine, 8-hydroxy-N⁶-methyladenine, aziridinylcytosine, 2-aminopurine or 2,6-diaminopurine.--

Remarks

The claims were amended to remove language which was held not expressly supported by the specification or to correct an error in the claims presentation that was submitted in paper No. 14. Support for new claims 43-46 is at page 3, lines 4-16 and page 4, lines 17-21. No new matter has been introduced.

Rejection under 35 USC §103

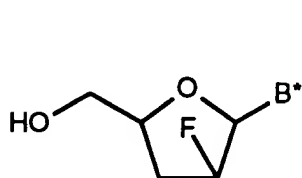
Claims 7-18, 20, 22 and 27-42 were rejected as allegedly prima facie obvious over Martin or Robins or Ranganathan or Webb or Tisdale in view of Padyukova or Montgomery. The Office held that the primary references disclosed "unphosphorylated nucleosides" corresponding to the claimed nucleotide analogs and that the secondary references disclosed 5'-methylene phosphonate derivatives of certain nucleosides.

In supporting the rejection, the Office asserted that it was obvious "either 1) to create 5'-nucleoside analogs that would circumvent cells resistant to the free drug [caused] by a lack of phosphorylating enzymes and/or 2) to incorporate said nucleoside analogs into oligonucleotides which then become resistant to nuclease digestion." Applicant respectfully traverses the rejection.

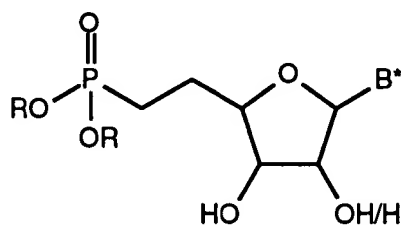
In order to maintain a rejection under section 103, the Office is obliged establish a case of prima facie obviousness. In re Fine 5 USPQ2d 1596 (Fed Cir 1988), 837 F.2d 1071. In establishing prima facie obviousness, the Office must show some objective teaching in the cited references that would lead an individual to combine the relevant teachings as evidence of obviousness. In re Lalu 223 USPQ 1257 (Fed Cir 1987). Both the suggestion and the expectation of success must be founded in the cited art, not in the applicant's disclosure. In re Dow Chemical Co. 5 USPQ2d 1529 (Fed Cir 1988). Hindsight reconstruction using applicant's disclosure and claims cannot be used as a guide to pick and choose among isolated elements to arrive at the claimed invention. In re Fine. In determining the scope and content of the cited art,

the references must be considered in their entirety, as a whole, including portions that lead away from the claimed invention. In re Panduit 1 USPQ2d 1593 (Fed Cir 1987). A reference cited in support of a rejection under section 103 is not properly cited if the reference is from a field of endeavor that is different from the inventor's field and if the reference is not reasonably pertinent to the particular problem with which the inventor is involved. In re Clay 23 USPQ2d 1058 (Fed Cir 1992), In re Deminski 230 USPQ 313 (Fed Cir 1986), 796 F.2d 436, 442. The purposes of both the invention and the cited reference are important in determining whether the reference is reasonably pertinent to the problem the invention attempts to solve. In making a determination that a reference is properly cited, the similarities and differences in structure and function between the reference and the claimed invention must be considered. In re Clay, In re Ellis 177 USPQ 526, 527 (CCPA 1973).

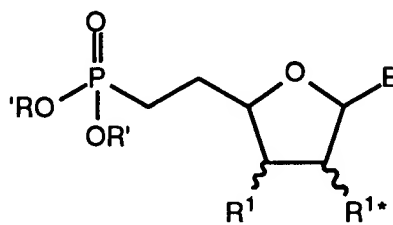
In defining the rejection asserted by the Office, the references are analyzed according to the structures relevant to the analysis. The closest primary and secondary reference structures are shown with corresponding claimed compounds.



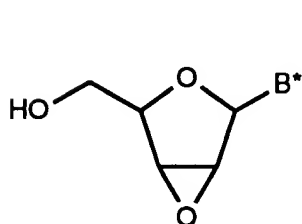
Martin
B* = U, C, 5-FC



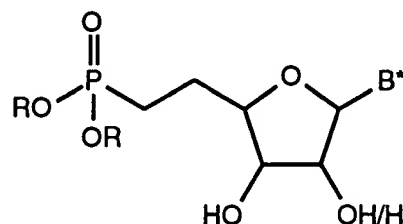
Padyukova/
Montgomery
B* = A, A^{bz}, U, 5-FU



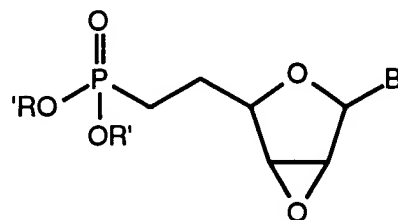
amended claim 7
R¹ = H, OH
R^{1*} = F, OCH₃



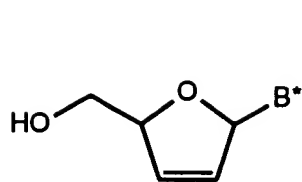
Robins
B* = A, A^{piv}, A^{bz}



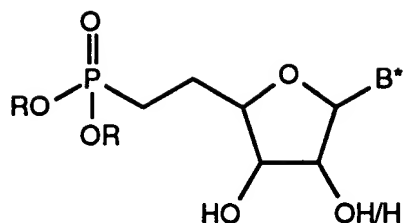
Padyukova/
Montgomery



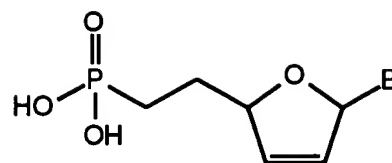
claim 8



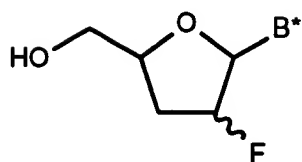
Martin
B* = 5MeC



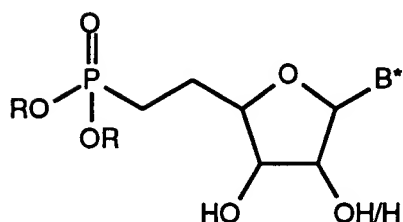
Padyukova/
Montgomery



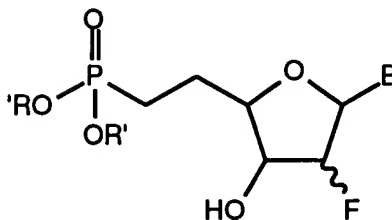
claim 9



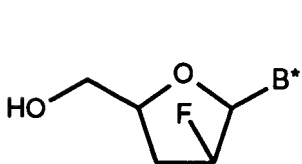
Ranganathan/
Webb/Tisdale
B* = A, G, DAP, Hx,
aziridinylC



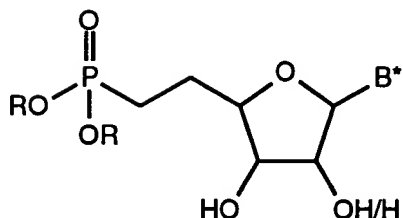
Padyukova/
Montgomery



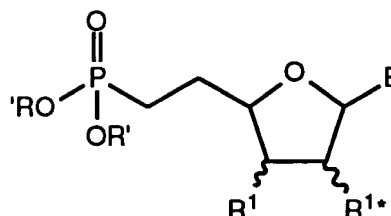
claim 10 and 14



Martin
B* = U, C, 5-FC



Padyukova/
Montgomery



amended claim 40

R¹ = F, OCH₃

R^{1*} = H, OH, F, OCH₃

Comparing the primary reference structures with the compounds of claims 7-10 and 14 (other rejected claims are dependent on these claims) shows that the primary reference compounds are not simply "unphosphorylated nucleosides" that correspond to the claimed compounds. The phosphorylated derivatives of the primary reference compounds are phosphate nucleotide analogs which differ significantly from the claimed phosphonates.

None of the primary references suggest using any phosphonate analog for any purpose. Each reference addressed different issues. For example,

Martin was primarily concerned with the effect of fluorine atoms at the 2' and/or 3' positions of pyrimidine dideoxyribonucleosides which were characterized as inhibitors of HIV reverse transcriptase. Robins described adenosine 2',3'-ribo-epoxide synthesis primarily as an intermediate for synthesis of certain adenosine nucleoside analogs. No other use for the epoxides was suggested. Ranganathan described an improved synthetic route for certain 2'-substituted-2'-deoxyadenosine analogs which were described as potential antiviral or antitumor agents. Webb was concerned with incorporation of nucleotide analogs having an alkylating pyrimidine base into oligonucleotides. Tisdale described 2'-fluoro substituted purine nucleosides that were characterized as compounds useful for treating certain protozoa and certain viruses associated with respiratory tract infections.

The Padyukova secondary reference described phosphonate compounds as inhibitors of enzymes whose substrates are esters of phosphoric acid. There was no suggestion to use the compounds as antitumor or antiviral agents and there was no biological data presented to indicate any efficacy for any purpose. Padyukova was thus fairly characterized as disclosing an improved method to synthesize certain phosphonate nucleoside analogs that were suggested to be useful in oligonucleotide synthesis, but did not, by a showing of any data, invite or motivate further efforts toward phosphonate nucleoside analogs or phosphonate oligonucleotides.

The Montgomery secondary reference described the synthesis of the 5'-methylene phosphonate analog of 2'-deoxy-5-fluorouridylic acid as an analog of 5-fluorouracil, a compound characterized by Montgomery as having anticancer activity. Based on a reading of Montgomery it was unclear if , the phosphonate analog had any useful activity at inhibiting the target thymidine synthetase enzyme; preincubation of the disclosed compound with the enzyme prior to exposure of the enzyme to substrate was required to demonstrate enzyme inhibition in in vitro enzyme assays. Cytotoxicity of the compound was described by Montgomery as "moderately cytotoxic" (page 110, first column) and the mechanism of such toxicity was not ascribed to inhibiting the target enzyme. The compound was thus fairly characterized as likely to be ineffective as a therapeutic agent and thus taught away from the

use of the phosphonate compound. There was no suggestion to use the disclosed compound or any other phosphonate as an antiviral agent or in oligonucleotides and the compound itself did not invite or motivate further efforts toward phosphonate nucleoside analogs or phosphonate oligonucleotides.

In applying the analysis to the rejection of claims 7, 9 and 40, applicant submits that, under In re Clay neither secondary reference is properly combined with Martin and further, that the secondary references are not properly combined with each other. Martin, which deals with the field of antiviral agents, is outside the field addressed by either Montgomery (antitumor agents) or by Padyukova (phosphate esterase inhibitors or oligonucleotides). Selecting these references and combining them requires crossing from one field of endeavor to another to reach the claimed compounds. Arriving at this combination requires hindsight reconstruction based on applicant's disclosure which is impermissible. In re Fine. Assuming arguendo, that the references were properly combined, no motivation to arrive at the claimed compounds was found in any of them. Montgomery would have led one away from phosphonates, Padyukova did not lead one anywhere because no data was presented and Martin was silent about phosphonates. The cited references simply did not provide a basis for motivation when the references are considered as a whole as required. In re Panduit. Neither the objective teaching as required under In re Lalu nor the suggestion and expectation of success as required under In re Dow Chemical Co. is found in any of the references.

The Office stated that motivation to arrive at the compounds was present because "5'-nucleoside analogs would circumvent cells resistant to the free drug [caused] by a lack of phosphorylating enzymes". The statement supporting the conclusion of motivation is traversed because neither Martin, Montgomery nor Padyukova mention the use of any phosphonate as a substrate for any phosphorylating enzyme, i.e., a kinase. In fact, none of the cited references suggest the use of any phosphonate as a kinase substrate. This is the teaching of applicant's specification at page 6, lines 6-9, and as such, drawing this particular conclusion must be based on hindsight reconstruction using the specification.

Assuming that a suggestion to use a phosphonate nucleoside analog as claimed in the present specification as a substrate for an intracellular kinase was found in the cited references, which is not the case, it would not have been reasonably predictable that such compounds would have functioned as substrates for intracellular kinases. Attention is drawn to the reference by Kim et al (J Med Chem (1990) 33:1207-1213, newly cited) which shows that closely related acyclic phosphonate structures 1 and 8 of Table IV (page 1210, second column) have vastly different properties for guanylate kinase as shown in Table III (page 1210, first column). In relation to the compound under study and its analogs, Kim states at page 1210, second column, that isosteric and isoelectronic similarity between a potent compound and an analog are not sufficient for good activity, i.e., it cannot be easily predicted that a given compound will be a good kinase substrate. When viewed in this light, the teaching and claims found in applicant's specification cannot be obvious.

Applying the analysis under section 103 to the rejection of claim 8, applicant again submits that as discussed above, under In re Clay neither secondary reference is properly combined with Robins and further, that the secondary references are not properly combined with each other. Robins deals with the field of nucleoside analog synthesis and is outside the field addressed by either Montgomery (antitumor agents) or by Padyukova (phosphate esterase inhibitors or oligonucleotides). Selecting these references and combining them requires crossing from one field of endeavor to another to reach the claimed compounds. Arriving at this combination requires hindsight reconstruction based on applicant's disclosure which is impermissible. In re Fine. Again, assuming arguendo, that the references were properly combined, no motivation to arrive at the claimed compounds was found in any of them for the reasons previously discussed. Montgomery would have led one away from phosphonates, Padyukova did not lead one in any particular direction because no data was presented and Robins was silent about phosphonates. The cited references simply did not provide a basis for motivation when the references are considered as a whole as required. In re Panduit. Neither the objective teaching as required under In re Lalu nor the

suggestion and expectation of success as required under In re Dow Chemical Co. is found in any of the references.

The rejection of claims 10 and 14 should properly be withdrawn for reasons similar to those discussed under claims 7-9 and 40. The Tisdale reference is not properly combined with either secondary reference because it is outside the fields of the secondary references. In re Clay. Arriving at the claimed compounds using the cited references requires applicant's disclosure to pick out the needed structures. Webb and Padyukova both relate to oligonucleotides, but together provide no motivation to arrive at the claimed compounds. Under In re Clay, Montgomery is not properly combined with Webb. Both the objective teaching as required under In re Lalu and the suggestion and expectation of success as required under In re Dow Chemical Co. is lacking in the references. Finally, Ranganathan and Montgomery both relate to antitumor agents, but these references together provide no motivation to arrive at the claimed compounds. Under In re Clay, Padyukova is not properly combined with Ranganathan. Again, the objective teaching as required under In re Lalu and the suggestion and expectation of success as required under In re Dow Chemical Co. is lacking in the references because the Montgomery compound was not effective.

In view of the foregoing discussion, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 112(a)

Claims 7-18, 20, 22 and 27-42 were rejected based on an objection to the specification which was not held to support the negative proviso inserted into claim 7 by paper No. 14. Amended claim 7 removes the proviso. The objection and rejection should be moot. Reconsideration and withdrawal of both are requested.

Rejection under 35 USC 112(b)

Claims 7-18, 20, 22 and 27-42 were rejected based on applicant's previous improper amendment to claims 7, 10, 14, 20, and 38-42, which had chemical structures inserted as a taped piece of paper. Claims 7, 10, 14, 20, and

38-42 have been amended to properly present the claims. This rejection should now be moot. Applicant apologizes for any inconvenience to the Examiner caused by this error.

The Office indicated that no references were received on either of two occasions in connection with applicant's IDS submitted on March 15, 1993. Copies of the cited references will be included in a separate paper.

Conclusion

In view of the above amendments and remarks, the application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent at 415-573-4712 (Fax 415-573-4899).

Respectfully submitted,



Daryl D. Muenchau, Reg. No. 36,616
Gilead Sciences, Inc.
353 Lakeside Drive
Foster City, CA 94404

Dated: December 9, 1993